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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/593,217	09/15/2006	Ivan King	891-A-PCT-US	7034

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EXAMINER	
KRISHNAN, GANAPATHY	

ART UNIT	PAPER NUMBER
1623	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/593,217	KING ET AL.	
	Examiner	Art Unit	
	Ganapathy Krishnan	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/14/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. *11/20/2008* .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed 8/14/2008 has been received, entered and carefully considered. The following information provided in the amendment affects the instant application:

1. Claims 1-33 have been canceled.

2. New Claims 34-48 have been added.

3. Remarks drawn to rejections under 35 USC 112, first and second paragraphs and 103.

Claims 34-48 are pending in the case.

The following rejections have been rendered moot by cancellation of the said claims:

The objection to claim 15

The rejection of claims 17-18

The rejection of Claims 1-12 and 14-21 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention and

The rejection of Claims 1-12 and 14-21 under 35 U.S.C. 103(a) as being unpatentable over Lee et al (International Journal of Toxicology, 2002, 21, 23-38; cited in the ISR of 10/19/2006) in view of Gourdeau et al (US 6,630,480) and Hausheer et al (US 5,919,816).

Claim Objections.

The objection to claim is being maintained for reasons of record. Applicants have to recite the chemical name for the notation VNP40101M followed by the notation in parentheses at the first occurrence of the said notation.

The following new 35 USC 112 and double patenting rejections are made of record.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 34-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for combination of VNP40101M with cytarabine (AraC) and fludarabine in the specific dosages recited in Table 2 (page 13) and Table 3 (page 14) of the specification which would produce a synergistic effect on treating tumor, does not reasonably provide enablement for any other dose levels of the combination of VNP40101M with cytarabine (AraC) and fludarabine that is outside the recited ranges in the specification to produce a synergism on treating tumor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

A conclusion of lack of enablement means that, based on the evidence regarding each of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

(A) The breadth of the claims
(B) The state of the prior art
(C) The level of predictability in the art
(D)The amount of direction provided by the inventor
(E) The existence of working examples
(F) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims

Claims 34-48 are drawn to a synergistic combination of VNP40101M with an amount of cytarabine and fludarabine and methods of treating tumor in a subject using the combination. The terms, 'an amount' is seen to include any amount of the said active agents in a synergistic combination.

The state of the prior art

The examiner notes that prior art Gourdeau et al (US 6,630,480) and Hausheer et al (US 5,919,816) teach the use of nucleosides for the treatment of tumors and leukemias and that they can be combined with other antitumor agents. There is no teaching of potential synergistic combinations in a any dosage amount comprising nucleosides with other therapeutic agents. It is well known that the synergism is dosage and administration schedule dependent.

The level of predictability in the art

The instant claimed invention is highly *unpredictable*. It is also known in the art that synergistic or super additive effects for combinations of compounds in any amount are highly unpredictable. There is not seen sufficient data to substantiate synergistic combinations of antitumor agents with nucleosides in any amount as instantly claimed. Based on the teachings of the prior art it is highly unpredictable as to what dosages of the therapeutic agents will produce a synergistic combination for the treatment of tumors.

The amount of direction provided by the inventor

The instant specification is not seen to provide enough guidance that would allow a skilled artisan to extrapolate from the disclosure and the examples provided to enable synergistic compositions and their use in methods of treatment as instantly claimed. The specification also

fails to direct the skilled artisan in correlative prior art procedures which might provide the basis for predicting such combinations. The specification (pages 2-4 and 7) mentions references for the instant active agent VNP40101M and other potential chemotherapeutic agents including nucleosides and their use for the treatment of tumors.

The existence of working examples

The working examples set forth in the instant specification are drawn to synergistic combinations of the instant active agent, VNP40101M 5-10mpk, with cytarabine 50mpk and fludarabine 70mpk (Tables 2 and 3 at pages 13-14 of the specification). The dosages cited in these examples is not representative of synergism between the active agent combinations in any amount as broadly encompassed by the instant claim recitation. Applicants are therefore not entitled to claim synergistic combinations of VPN40101M with cytarabine and fludarabine in any dosage range other than the dosages cited in the instant examples.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure

Indeed, in view of the information set forth, the instant disclosure is not seen to be sufficient to enable the synergistic compositions and their use in method s of treatment as instantly claimed. One of ordinary skill in the art would have to make compositions containing several different dosages of the active agents in order to determine which of their dosage amounts produce synergism. Undue experimentation is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or

improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 34-48 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 70-73 of U.S. Patent No. 6,855,695 ('695). Although the conflicting claims are not identical, they are not patentably distinct from each other because:

Instant Claims 34-35 are drawn to a composition comprising and amount of VPN 40101M in combination with cytarabine and fludarabine respectively. Claims 36-48 are drawn to method of treatment of tumors using the above composition.

Claims 70-73 of '695 are also drawn to compositions and method of treating tumor comprising substituted hydrazines and another antitumor agent including cytarabine.

Claims 70-73 of '695 differ from the instant claims in that the instant claims employ only cytarabine and fludarabine as additional agents and also employ substituted aryl derivatives of VNP40101M. However, it would have been obvious to one of ordinary skill in the art at the time

the invention was made that substituted aryl derivatives of VNP40101M in combination with cytarabine and fludarabine could be successfully employed in the method of '695.

In determining the differences between the prior art and the claims, the question is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. "The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." *In re Kotzab*, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000). In the instant case, '695 teaches performing each of the steps applicant claims. Although the claims of '695 employ a structurally modified analog of VNP40101M, one of ordinary skill in the art would readily recognize that the scheme taught by '695 could be employed in making and using the parent compound in combination with the nucleosides as instantly claimed. The use of known members of classes of active agents in compositions and methods of use taught in the prior art is not seen to render the instantly claimed compositions and method unobvious over the art. Once the general active agent and method of use has been shown to be old, the burden is on the applicant to present reason or authority for believing that a structural modification of the starting compound would alter the nature of the product and thus the unobviousness of the method of using it.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 34-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (International Journal of Toxicology, 2002, 21, 23-38; cited in the ISR of 10/19/2006) in view of Gourdeau et al (US 6,630,480), both of record.

Lee et al teach that 1, 2-bis (methylsulfonyl)-1-(2-chloroethyl)-2-(methylaminocarbonyl) hydrazine (also abbreviated as VNP40101M) is a novel alkylating antitumor agent (abstract; page 23, right column, first paragraph). It has been shown to possess a broad spectrum of antitumor activity including solid tumors and leukemia (page 24, left column, middle paragraph). It has also been found to be superior to many other antitumor agents. Lee also teaches maximum tolerated doses of the agent. However, Lee et al do not suggest a combination of the compound with a nucleoside or a nucleoside analog and the use of the combination and another therapy for the treatment of tumors.

Gourdeau et al teach the use of cytosine analogs and cytarabine for the treatment of leukemia and chronic myelogenous leukemias (abstract; col. 5, line 10 through col. 7, line 56; col. 10, line 44 through col. 11, line 35). According to Gourdenau standard treatment for leukemia involves chemotherapy and/or radiation therapy and chemotherapy includes treatment with two or more anticancer drugs (col. 1, lines 55-63). Currently the most important nucleosides that are used for the treatment of leukemia include cytarabine and fludarabine (col. 2, lines 28-32).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make compositions of VNP40101M and a nucleoside or nucleoside analog and use the combination in methods of treatments as instantly claimed since compositions comprising the individual active agents and their use for the treatment of tumors, cancers and leukemias is seen to be taught in the prior art.

It has been held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to form a third composition

that is to be used for the very same purpose. The idea of combining them flows logically from their having been taught individually in the prior art. See In re Kerkhoven, 205 USPQ 1069, CCPA 1980.

It is well within the skill level of the artisan to adjust the dosage level of the active agents in order to obtain maximum beneficial effects.

The following new art rejection is made of record.

Claims 34-48 are rejected under 35 U.S.C. 103(a) as being obvious over Lin et al (US 6,855,695), newly cited.

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Lin et al, alkylating agents, teach derivatives of VNP40101M (closely related structural analogs) of formula I for the treatment of tumors and cancers (col. 3, line 44 through col. 5, line 40; col. 8, lines 43-45). The compounds of their invention can also be administered with other antitumor agents that may act synergistically, including cytarabine (AraC). The synergism can be unexpected (col. 14, lines 35-67).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use VNP40101M in combination with cytarabine and fludarabine to a synergistic composition and use the composition in a method of treatment of tumors as instantly claimed since such a composition and method of treatment is suggested using closely analogous derivatives of VNP40101M.

One of ordinary skill in the art would be motivated to make and use such a composition since the antitumor activity of the parent compound and closely related structural analogs and their synergism, which may be unexpected, is suggested in the prior art. Since Lin teaches that their compounds can be administered with other conventional cancer therapies (col. 13, lines 32-34) and possible synergistic combinations, one of skill in the art would look for such combinations of VNP40101M with cytarabine (AraC) and the related fludarabine for combinations that have highly synergistic effects. Similarity in structure and function also entails motivation for making such compositions and using them in method of treatment as instantly claimed.

Response to Applicants Arguments

Applicants have presented new composition claims 34-35 that is drawn to a synergistic combination of the active agents that are used in the examples. The enablement rejection above

is made of record for lack of synergism between the active agents in any amount as broadly claimed. The method claims are drawn to the treatment of tumors using a combination of the said active agents in an effective amount, for which the rejection under 35 USC 103(a) as above is being maintained. Even if applicants intend a synergistic combination of the active agents in the instant method claims, synergism is enabled for the method claims only in the dosages recited in Table 2 (page 13) and Table 3 (page 14) of the specification.

Conclusion

Claims 34-48 are rejected

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathy Krishnan whose telephone number is 571-272-0654. The examiner can normally be reached on 8.30am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ganapathy Krishnan/

Examiner, Art Unit 1623

/Shaojia Anna Jiang/

Supervisory Patent Examiner, Art Unit 1623